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Atopic Dermatitis, Depression, and Suicidality

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Abstract

Atopic dermatitis (AD) is a common disease associated with an underappreciated increased risk of depression and suicidality. Current literature investigates associated risk factors, including severity of disease, age, sex, and atopic comorbidities, which may help identify patients with AD at high risk for depression or suicidality. Increasing severity of AD and female sex are associated with an increased risk for both depression and suicidality, while increasing age is associated with an increased risk for depression only. Further research is required to validate the studies supporting these reported associations with a particular emphasis on suicidality and AD due to lack of information. The use of these risk factors may assist in the creation of simple screening tools to screen for psychiatric comorbidity in patients with AD.

Keywords

dermatitis, atopic, depression, suicide, suicidal ideation, attempted suicide, risk factors

Atopic dermatitis (AD) is the most common chronic inflammatory disease of childhood with a global prevalence in children as high as 20%.[1] Primarily a disease of childhood, a recent systematic review and meta-analysis showed that the disease on average persisted for 6.1 ± 0.02 years (mean ± standard error) after onset.[2] However, about 5% of participants had atopic dermatitis persisting for 20 years after onset, well into their adult years.[2]

Although AD is associated with physical comorbidities, such as other atopic diseases like allergic rhinitis and asthma, and metabolic syndrome,[3,4] there is an underappreciation of the associated psychiatric comorbidities, particularly depression and suicidality, defined here as suicidal ideation and attempted or completed suicide. Although many dermatological diseases have been linked to psychiatric comorbidities, patients with atopic dermatitis were noted 50 years ago to have a characteristic psychological profile, one high in anxiety and depression, that differs from patients with other cutaneous diseases.[5]

The cause of AD consists of defects in the skin barrier primarily through disruption of filaggrin and alterations of the innate and acquired immune system, including inflammatory cells and markers, particularly interleukin (IL) 4 and 13 expression. A number of potential theories exist as to why patients with AD have a higher risk of psychiatric illness. First, it is possible that these changes in inflammatory markers are what contribute to psychiatric illness in patients. Other inflammatory skin diseases, such as psoriasis, link the inflammatory pathways involved in the disease with depression. This association, for instance, can be seen in patients with psoriasis treated for hepatitis C with the proinflammatory cytokine interferon (IFN) as the IFN both exacerbates psoriasis symptoms and causes depression as a frequent side effect.[6,7] Furthermore, biologics used for psoriasis that block certain inflammatory markers involved in both depression and psoriasis have been shown to reduce the rates of depressive symptoms.[8-10] It is possible that the alteration in the cytokine profile of AD may contribute to the increased risk of depression, much like it does in psoriasis. Second, there is a well-known link between sleep disturbance and depression in the general population.[11] A number of studies show an increase in sleep disturbances in patients with AD compared to nonatopic patients,[12-14] which may contribute to an increased risk of depression. Third, pruritus is a major symptom of AD. It is known that depression[15] and even suicidal ideation[16] in AD are associated with itch, and increasing severity of itch is associated with increasing severity of depression.[17]

Targeting these three factors—inflammatory pathways, sleep disturbances, and itch—is associated with a decrease in depression in patients with AD. Dupilumab, a monoclonal antibody that blocks the activity of IL-4 and IL-13 through inhibition of their receptor, has shown excellent efficacy with a good safety profile in treating moderate to severe AD resistant to topical therapies.[18,19] Along with blocking inflammatory

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Table 1. Associations Found in Patients With Atopic Dermatitis With Depression and Suicidality.

	Association	Selected References
Depression		
Atopic Dermatitis Overall	Increased compared to controls	21, 25, 26,42
Atopic Dermatitis Severity	Increased with increasing severity	25, 28, 29
Sex	Increased in females	30-32
Age	Increased with increasing age[a]	33
Atopic Comorbidities	No significant association	33
Suicidality		
Atopic Dermatitis Overall	Increased compared to controls	36, 37, 42
Atopic Dermatitis Severity	Increased with increasing severity	39
Sex	Increased in females[a]	16, 32
Age	No studies completed	
Atopic Comorbidities	No studies completed	

[a]Associations were close to but did not reach statistical significance

markers, patients using dupilumab report significant reduction in pruritus and significant improvement in sleep.[18-20] At the same time, dupilumab has been shown to significantly improve the psychiatric symptoms of depression and anxiety, as measured by the Hospital Anxiety and Depression Scale (HADS) after 16 weeks of therapy.[18-20] Although this may provide evidence for the etiology of increased depression in patients with AD, further research is required to confirm the associations as well as potential causality between inflammatory markers, sleep, itch, and depression in AD.

Association of Depression and Suicidality in AD

To evaluate the association of depression and suicidality in patients with AD, we performed a Medline search using the following keywords: *atopic dermatitis*, *eczema*, *depression*, *suicide*, *attempted suicide*, and *suicidal ideation*. The overall association between AD and depression or suicidality found in the literature, as well as specific risk factors—namely, severity of disease, sex, age, and atopic comorbidities—is summarised in Table 1 and discussed below.

AD and Depression

AD significantly affects a patient's mental health. A study looking at 5555 US adults included in a 2005 to 2006 National Health and Nutrition Examination Survey (NHANES) showed a prevalence of AD of 6.2% (95% confidence interval [CI], 5.6%-6.8%).[21] Thirty-one percent of the participants with AD reported at least one symptom of depression. There was a high prevalence of reports from AD participants feeling depressed or hopeless, having fatigue, having poor or increased appetite, or feeling bad about themselves nearly every day.[21] Other studies have shown additional distress in those with AD such as increased social isolation,[22] emotional deprivation,[22] and a loss of meaning in one's life.[23] The NHANES assessed the association between AD and depression using two different diagnostic criteria.[21] Based on Sleep, Interest, Guilt, Energy, Concentration, Appetite, Psychomotor, and Suicidality (SIGECAPS) criteria, a tool that diagnoses depression if 4 of 8 depressive symptoms in combination with depressed mood are present for at least two weeks,[24] participants with AD had an increased risk of depression after adjustment for demographics and comorbidities (odds ratio [OR], 1.89; 95% CI, 1.28-2.77). Using the validated Patient Health Questionnaire 9 (PHQ-9) screening tool, which further classifies depression into mild, moderate, and severe, there was a significantly increased risk of moderate (OR, 1.97; 95% CI, 1.10-3.51) and severe (OR, 4.64; 95% CI, 2.46-8.75) depression in participants with AD. Mild depression was increased in AD compared with controls; however, this result was not statistically significant (OR, 1.46; 95% CI, 0.91-2.36).[21] The increased risk of depression is found not only in lifetime risk but previous year risk as well. The same study examined the responses from 34 613 US adults from the 2012 National Health Interview Survey with a self-reported prevalence of AD in 7.2% (95% CI, 6.9%-7.6%) of participants.[21] Health care provider-diagnosed lifetime depression prevalence (OR, 2.29; 95% CI, 2.02-2.61) and prevalence over the past year (OR, 2.31; 95% CI, 2.00-2.66) were significantly increased in participants with AD.[21] The increased previous year risk of depression in adult patients with AD is also supported by the 2013 US National Health and Wellness Survey (NHWS), which looked at 75 000 US adults, of whom 428 self-reported having AD over the previous year.[25] There was a statistically significant increase in depression rates in the participants with AD (37.2%) compared to those without AD (20.9%).[25] Another study has verified this increased risk of depression in adolescents with AD as well,[26] although the relationship is not consistent between different teenage populations.[27]

Disease Severity

A cross-sectional study in Korea looked at data from 120 508 adult men, of whom 1517 had AD diagnosed by a dermatologist.[28] Adjusting for age, level of education, economic status, family structure, and other psychological distress, the odds ratio for depression in participants with AD compared to those without AD was 1.79 (95% CI, 1.40-2.29).[28] Using the eczema area and severity index (EASI) scoring system, which looks at both percentage of skin affected and the severity of AD in four body regions, the participants were divided into 192 participants with moderate to severe AD and 1323 participants with mild AD (sample sizes estimated using percentages disclosed in manuscript, subject to rounding errors). The authors of the study found a greater relationship with depression in moderate to severe AD (OR, 2.25; 95% CI, 1.20-4.20) compared to mild AD (OR, 1.72; 95% CI, 1.32-2.24) although not statistically significant.[28] This greater relationship was also found in US adults. The 2013 US NHWS study showed self-reported classification of their 428 US adults with AD over the previous year based on disease severity, with 182 participants having mild disease, 148 having moderate disease, and 36 having severe disease.[25] The study showed higher rates of depression in moderate to severe AD (39.4%) compared to mild AD (34.6%), although the difference was not statistically significant.[25]

Another cross-sectional study looked at 79 667 US children aged 0 to 17 years who had presented to a health care provider in 2007; 13% had AD or approximately 10 341 (sample size estimated using percentage disclosed in manuscript, subject to rounding errors).[29] Compared to the control population, the children with AD had an increased risk of ever having depression (OR, 2.00; 95% CI, 1.49-2.69) and an increased risk of currently having depression at the time of presentation to a health care provider (OR, 2.28; 95% CI, 1.55-3.35). The authors of the study also compared mild, moderate, and severe AD in participants, with approximately 67% of the children having mild disease, 26% having moderate disease, and 7% having severe disease. There was a statistically significant increase in depression rates with increasing severity of AD: none (3.7%), mild (5.4%), moderate (7.2%), and severe (14.1%).[29]

Sex

The Northern Finland 1966 Birth Cohort study gathered data on all live infant births (12 058) in 1966 prospectively until the children reached the age of 31 years. Studies using this data examined the association of atopy (positive skin prick test to at least one of three common allergens and clinical symptoms of at least one of AD, asthma, allergic rhinitis, and allergic conjunctivitis) and depression in these participants.[30,31] Depression was categorised into three different severities based on the Hopkins' Symptom Checklist 25 (HSCL-25). The studies found that atopic females had an increased odds ratio of having any severity of depression compared to nonatopic females, while the increased odds ratio was only present in severe depression for atopic males.[30,31] With a focus on AD, a recent small cross-sectional study looked at 45 females and compared them to 36 similarly aged males with AD.[32] Through screening with the PHQ-9 questionnaire, there were significantly higher depression scores in females compared to males, with only 26.7% of females having a PHQ-9 score of 0 to 4 (no depression) compared to 63.9% of males.[32] Larger population-based studies specifically focusing on patients with AD are needed to confirm the association of increased depression in females compared to males.

Age

A longitudinal study in Taiwan looked at 8208 patients with AD older than 12 years without a psychiatric history and age/sex matched them (1:1) with a control population also without a psychiatric history.[33] These patients were enrolled in the study between 1998 and 2008 and followed to the end of 2011. After adjustment for a number of factors, compared to controls, patients with AD had a significantly elevated risk of developing major depressive disorder (hazard ratio [HR], 6.56; 95% CI, 3.64-11.84). The authors further divided their patients into 1568 adolescents (<18 years old at the time of enrollment) and 6640 adults (≥18 years old at the time of enrollment). Adults showed greater increased risk of major depressive disorder (HR, 7.56; 95% CI, 3.75-15.23) compared to adolescents (HR, 4.26; 95% CI, 1.39-13.13), a result that was close to but did not reach statistical significance.[33]

Atopic Comorbidities

AD is associated with a number of atopic comorbidities. Best known is the atopic triad of AD, asthma, and allergic rhinitis, with one study reporting a 71.3% prevalence of asthma or allergic rhinitis in children with AD.[34] However, the previously mentioned Taiwanese longitudinal study did not find any relationship of major depressive disorder with associated asthma (HR, 1.61; 95% CI, 0.87-2.96), allergic rhinitis (HR, 1.15; 95% CI, 0.74-1.77), or allergic conjunctivitis (HR, 1.18; 95% CI, 0.75-1.85).[33]

AD and Suicidality

The association between AD and suicidality, defined here as suicidal ideation and attempted or completed suicide, has not been as thoroughly investigated as the association between AD and depression. One of the earliest studies investigating this relationship was the study by Gupta and Gupta[35] that merged data from several large studies, creating a sample of 146 patients with mild and moderate AD. This study found approximately 2.1% of patients with AD having active suicidal ideation and 2.7% endorsing a wish

to be dead. However, there was no comparison to healthy controls in this study.[35] A study by Zachariae et al[36] aimed to quantify the suicidal ideation of patients with AD and compare the rate to healthy controls. A sample of 95 inpatient and outpatient patients with AD compared to age-, sex-, and country-matched healthy controls showed a statistically significant increase in suicidal thoughts (18.9%) in patients with AD compared to controls (6.8%).[36] The suicidal rates found here were much higher than those of the study by Gupta and Gupta, which has been attributed to the low severity of AD in the patients reported in that study. A recent population-based study took 7663 Danish participants with a dermatologist-made diagnosis of AD between 1997 and 2011 and compared them to 37 924 age-, sex-, and calendar time-matched controls from the general population. The study found that although self-harm and suicide attempts were not statistically increased in participants with AD (incidence rate ratio [IRR], 1.71; 95% CI, 0.77-3.83), the risk of physician-reported completed suicide was significantly higher in the AD population compared to the controls (IRR, 2.08; 95% CI, 1.03-4.21).[37] This IRR was not different than the increased risk of completed suicide found in the Danish population of 68 511 participants with mild or severe psoriasis also investigated in this study.[37] Psoriasis has been shown to cause significantly increased suicidality, particularly in its most severe form, highlighting the need for more recognition of the detrimental mental health effects of AD as well.[38]

Disease Severity

In regards to the association of suicidality and severity of AD, a study of both child and adult patients with AD compared self-reported suicidal thoughts with AD severity classified by the SCORing Atopic Dermatitis (SCORAD) index by a health care professional.[39] The SCORAD index uses area of disease, intensity of physical signs, and severity of subjective symptoms to classify the severity of AD. This classification yielded 2348 patients with mild AD, 2617 patients with moderate AD, and 1783 patients with severe AD. Compared to the 0.08% rate of suicidal ideation in a sample of 3575 healthy controls, the rates of suicidal ideation were higher in patients with AD and increased with increasing severity of AD, with rates of 0.2% of patients with mild AD, 6.0% of patients with moderate AD, and 19.6% of patients with severe AD.[39]

Sex

Sex and suicidality have not been investigated thoroughly for patients with AD. The previously mentioned cross-sectional study of 45 females and 36 males with AD asked each patient about suicidal ideation using the PHQ-9 screening tool.[32] Although 22.2% of females reported suicidal ideation compared to 8.3% of males, this was not statistically significant due to the small sample sizes.[32] A 2014 population-based study looked at 3775 adolescents (18-19 years) with no eczema history, previous eczema history, or current eczema history (eczema referring to AD in this study). The authors found a similar adjusted odds ratio between current eczema and suicidal ideation in boys (OR, 2.29; 95% CI, 1.18-4.44) and girls (OR, 1.74; 95% CI, 1.14-2.66), although overall, girls with current eczema reported higher rates of suicidal ideation (17.7%) compared to boys (10.8%).[16]

Age and Atopic Comorbidities

No studies were found regarding age or atopic comorbidities in patients with AD and their association with suicidality, suggesting a need for further research in this area.

Screening

Screening for depression and suicidality in AD may help identify patients at high risk for psychiatric comorbidities. However, currently available screening tools are lengthy, and thus more efficient tools are necessary to make screening for depression and suicidality feasible in a clinical setting. Recently, a simple screening algorithm using the PHQ-2, a validated tool that uses the first two questions of the PHQ-9 to screen for depressed mood and anhedonia,[40] has been used for identifying depression in patients with psoriasis.[41] The PHQ-2 screening tool may also be considered for patients with AD, although it would require validation before being used clinically. On the other hand, with further research into risk factors associated with depression and suicidality in patients with AD, other simple screening tools may be created specifically for patients with AD and applied in a clinical setting.

Conclusions

AD is a highly prevalent disease with an underinvestigated association of increased risk of depression and suicidality. Using risk factors may identify patients at higher risk for depression and suicidality. These risk factors include increasing severity and female sex for both depression and suicidality as well as increasing age for depression. Limitations of these conclusions include an insufficient number of currently available studies, particularly those regarding suicidality, and making conclusions on associations that came close to but did not reach statistical significance. Further research is required to validate the associations reported as many studies consist of small sample sizes that may not be generalizable to the entire AD population. There is also a need for further research in identifying additional risk factors that may play a role in creating effective and efficient screening tools for psychiatric comorbidity in patients with AD.

Declaration of Conflicting Interests

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